

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
14 February 2002 (14.02.2002)

PCT

(10) International Publication Number
WO 02/011766 A3

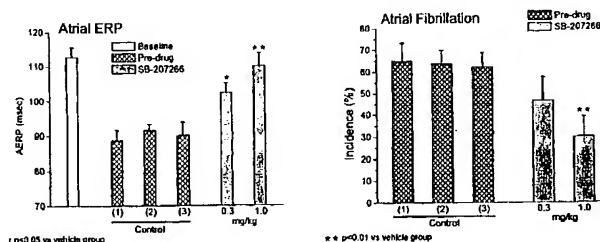
- (51) International Patent Classification⁷: A61K 45/08, A61P 9/06
- (21) International Application Number: PCT/GB01/03544
- (22) International Filing Date: 7 August 2001 (07.08.2001)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
- | | | |
|-----------|----------------------------|----|
| 0019410.0 | 7 August 2000 (07.08.2000) | GB |
| 0019523.0 | 8 August 2000 (08.08.2000) | GB |
| 0019524.8 | 8 August 2000 (08.08.2000) | GB |
| 0118919.0 | 2 August 2001 (02.08.2001) | GB |
| 0119022.2 | 3 August 2001 (03.08.2001) | GB |
- (71) Applicants (for all designated States except US): **LABORATOIRE GLAXOSMITHKLINE S.A.S.** [FR/FR]; 100 route de Versailles, F-78163 Marly-le-Roi Cedex (FR). **SMITHKLINE BEECHAM CORPORATION** [US/US]; One Franklin Plaza, P.O. Box 7929, Philadelphia, PA 19103 (US). **GLAXO GROUP LIMITED** [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).
- (72) Inventors; and
(75) Inventors/Applicants (for US only): **BONHOMME, Mireille, Marguerite, Jeanne** [FR/FR]; Laboratoire GlaxoSmithKline S.A.S., Centre de recherches, 25, avenue du Québec, F-91951 Les Ulis (FR). **BRIL, Antoine, Michel, Alain** [FR/FR]; GlaxoSmithKline Pharmaceuticals, 709 Swedeland road, King of Prussia, PA 19406 (FR). **GOUT, Bernard, Emile, Joseph** [FR/FR]; Laboratoire GlaxoSmithKline S.A.S., Unité de Recherche, 4, rue du Chesnay-Beauregard, B.P. 96205, F-35760 Saint-Grégoire (FR). **PATEL, Bela, Rajiv** [US/US]; GlaxoSmithKline Pharmaceuticals, 709 Swedeland Road, King of Prussia, PA 19406 (US). **SHEPHERD, Gillian, Louise** [GB/GB]; Glaxo Wellcome plc, 891-995 Greenford Road, Greenford, Middlesex UB6 0HE (GB).
- (74) Agent: **WATERS, David, Martin**; GlaxoSmithKline, Corporate Intellectual Property (CN9.25.1), 980 Great West Road, Brentford, Middlesex TW8 9GS (GB).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,

[Continued on next page]

(54) Title: USE OF 5HT₄ RECEPTOR ANTAGONISTS IN THE MANUFACTURE OF A MEDICAMENT FOR THE PROPHYLAXIS OR TREATMENT OF ATRIAL FIBRILLATION

Figure 3. 5-HT₄ antagonists in atrial fibrillation / atrial remodelling / atrial pacing

• SB-207266 treated group (n=7)



(57) Abstract: The invention relates to the use of a 5-HT₄ receptor antagonist in the manufacture of a medicament for the prophylaxis or treatment of atrial remodelling in a mammal. Preferably, the antagonist is N-[(1ⁿbutyl-4-piperidinyl) methyl]-3,4-dihydro-2H-[1,3]oxazino[3,2-a]indole-10-carboxamide (SB207266) or a pharmaceutically acceptable salt thereof. The invention also relates to the use of SB 207266 or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment or prophylaxis of atrial fibrillation in a mammal by administering to the mammal a daily oral or parenteral dosage regimen of about 0.2 mg to 1.0 mg of the SB 207266 or salt thereof per kg of total body weight (measured as the free base). The invention also relates to the use of SB 207266 or a pharmaceutically acceptable salt thereof in the prophylaxis or treatment of atrial arrhythmia in a mammal by administration of the SB 207266 or salt thereof on the first day at a loading dose of about 1.2 to about 2.0 times the daily maintenance dose, followed by administration of the SB 207266 or salt at the daily maintenance dose on subsequent days.

WO 02/011766 A3



MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

Published:

— with international search report

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(88) Date of publication of the international search report:

1 August 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

Declaration under Rule 4.17:

— as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/GB 01/03544

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 A61K45/08 A61P9/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, PASCAL, WPI Data, BIOSIS, MEDLINE, CHEM ABS Data, SCISEARCH, EMBASE PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
------------	--	-----------------------

X	WO 98 07728 A (FEDOULOFF MICHAEL ;GUEST DAVID WILLIAM (GB); SMITH GILLIAN ELIZABE) 26 February 1998 (1998-02-26) cited in the application * p.1-4; claims 1,7 *	3-5, 8-11, 14-19, 24,25, 28-34, 40-43, 46-48
X	WO 94 27965 A (SYNTEX INC) 8 December 1994 (1994-12-08) cited in the application claims 1-29	3-5, 8-10, 40-43, 46-48

-/--

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the International filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

Z document member of the same patent family

Date of the actual completion of the international search

25 January 2002

Date of mailing of the international search report

27/02/2002

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Uiber, P

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 01/03544

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 501 322 A (GLAXO GROUP LTD) 2 September 1992 (1992-09-02) cited in the application claims 1-16	3-5, 8-10, 40-43, 46-48
X	EP 0 732 333 A (LILLY CO ELI) 18 September 1996 (1996-09-18) cited in the application claims 1-7	3-5, 8-10, 40-43, 46-48
X	WO 93 05038 A (SMITHKLINE BEECHAM PLC) 18 March 1993 (1993-03-18) cited in the application claims 1-22	3-5, 8-10, 40-43, 46-48
X	WO 93 20071 A (GLAXO GROUP LTD ; OXFORD ALEXANDER WILLIAM (GB)) 14 October 1993 (1993-10-14) cited in the application claims 1-14	3-5, 8-10, 40-43, 46-48
X	WO 91 16045 A (SMITH KLINE FRENCH LAB) 31 October 1991 (1991-10-31) cited in the application claims 1-15	3-5, 8-10, 40-43, 46-48
Y	PIOT O ET AL: "Remodelage electrophysiologique induit par la fibrillation atriale: Curiosite experimentale ou determinant majeur de la fibrillation atriale chez l'homme ?" ARCHIVES DES MALADIES DU COEUR ET DES VAISSEAUX, 2000, 93, 7, XP001037264 the whole document	1-48

-/-

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 01/03544

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 9 November 1999 (1999-11-09) RAHME MARC M ET AL: "Electrophysiological and antiarrhythmic effects of the atrial selective 5-HT₄ receptor antagonist RS-100302 in experimental atrial flutter and fibrillation." Database accession no. PREV200000024149 XP002188320 abstract & CIRCULATION, vol. 100, no. 19, 9 November 1999 (1999-11-09), pages 2010-2017, ISSN: 0009-7322</p>	1-48

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 01/03544

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9807728	A	26-02-1998	AT 197588 T	15-12-2000
			AU 717177 B2	16-03-2000
			AU 4204897 A	06-03-1998
			BR 9711189 A	17-08-1999
			CN 1233250 A	27-10-1999
			CZ 9900516 A3	14-07-1999
			DE 69703554 D1	21-12-2000
			DE 69703554 T2	05-07-2001
			DK 922048 T3	08-01-2001
			WO 9807728 A1	26-02-1998
			EP 0922048 A1	16-06-1999
			ES 2151743 T3	01-01-2001
			JP 2000516240 T	05-12-2000
			NO 990697 A	15-02-1999
			PL 331647 A1	02-08-1999
			PT 922048 T	30-03-2001
			SI 922048 T1	28-02-2001
			TR 9900321 T2	21-04-1999
			TW 427990 B	01-04-2001
			US 6100397 A	08-08-2000
			ZA 9707302 A	15-02-1999
WO 9427965	A	08-12-1994	AT 171446 T	15-10-1998
			AU 680004 B2	17-07-1997
			AU 6954894 A	20-12-1994
			BR 9406724 A	06-02-1996
			CA 2163747 A1	08-12-1994
			CN 1124485 A ,B	12-06-1996
			CZ 9502780 A3	12-06-1996
			DE 69413535 D1	29-10-1998
			DE 69413535 T2	11-02-1999
			DK 700383 T3	14-06-1999
			EP 0700383 A1	13-03-1996
			ES 2121210 T3	16-11-1998
			FI 955660 A	24-11-1995
			HU 9500112 A3	28-06-1995
			HU 74870 A2	28-02-1997
			IL 109776 A	10-03-1998
			JP 8510743 T	12-11-1996
			NO 954761 A	26-01-1996
			NZ 267296 A	24-04-1997
			PL 311723 A1	04-03-1996
			WO 9427965 A1	08-12-1994
			US 5763458 A	09-06-1998
EP 0501322	A	02-09-1992	AP 295 A	29-12-1993
			AU 645402 B2	13-01-1994
			AU 1209492 A	15-09-1992
			DE 69213276 D1	10-10-1996
			DE 69213276 T2	23-01-1997
			WO 9214727 A1	03-09-1992
			EP 0501322 A1	02-09-1992
			ES 2091963 T3	16-11-1996
			FI 933697 A	23-08-1993
			HU 65486 A2	28-06-1994
			IL 101042 A	18-06-1996
			NO 933015 A	24-08-1993
			NZ 241704 A	25-11-1993

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 01/03544

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0501322 A		AT 142205 T CA 2105179 A1 IE 920567 A1 JP 6505238 T MX 9200762 A1	15-09-1996 26-08-1992 26-08-1992 16-06-1994 01-08-1992
EP 0732333 A	18-09-1996	US 5654320 A AT 203748 T AU 700842 B2 AU 6894896 A BR 9608223 A CA 2215359 A1 CN 1183041 A DE 69614164 D1 DK 732333 T3 EP 0732333 A1 ES 2159345 T3 HU 9801386 A2 JP 11502230 T NO 974221 A NZ 315971 A PL 322362 A1 SK 124297 A3 TR 9700956 T1 WO 9633713 A1 US 5798367 A US 5817676 A	05-08-1997 15-08-2001 14-01-1999 18-11-1996 29-12-1998 31-10-1996 27-05-1998 06-09-2001 08-10-2001 18-09-1996 01-10-2001 28-06-1999 23-02-1999 27-10-1997 28-01-1999 19-01-1998 04-02-1998 21-02-1998 31-10-1996 25-08-1998 06-10-1998
WO 9305038 A	18-03-1993	AT 182591 T AU 2491092 A AU 668102 B2 AU 2541892 A AU 691430 B2 AU 6073596 A BR 9206599 A CA 2118798 A1 CA 2118812 A1 CZ 9400560 A3 DE 69229674 D1 DE 69229674 T2 DK 604494 T3 EP 0603220 A1 EP 0604494 A1 ES 2135414 T3 FI 941178 A WO 9305040 A1 WO 9305038 A1 GR 3031462 T3 HU 70154 A2 JP 6510764 T JP 6510537 T MX 9205168 A1 MX 9205204 A1 NO 940874 A NZ 244282 A PT 100854 A PT 100855 A ,B SG 49153 A1	15-08-1999 05-04-1993 26-04-1996 05-04-1993 14-05-1998 03-10-1996 08-11-1994 18-03-1993 18-03-1993 13-07-1994 02-09-1999 06-04-2000 29-11-1999 29-06-1994 06-07-1994 01-11-1999 11-03-1994 18-03-1993 18-03-1993 31-01-2000 28-09-1995 01-12-1994 24-11-1994 01-03-1993 31-01-1994 11-03-1994 28-08-1995 29-10-1993 30-11-1993 18-05-1998

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 01/03544

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9305038	A	SK 30294 A3	07-12-1994
		US 5552398 A	03-09-1996
		US 5580885 A	03-12-1996
		ZA 9206889 A	24-05-1993
		ZA 9206890 A	14-06-1993
		AP 373 A	07-12-1994
		AU 2435092 A	16-03-1993
		AU 5194496 A	18-07-1996
		CA 2116024 A1	04-03-1993
		CN 1073173 A ,B	16-06-1993
		EP 0600955 A1	15-06-1994
		WO 9303725 A1	04-03-1993
		IL 103138 A	09-05-1999
		JP 6510283 T	17-11-1994
		MX 9204786 A1	01-04-1993
		NZ 243993 A	26-10-1994
		PT 100785 A	29-04-1994
		RU 2124512 C1	10-01-1999
		AU 3457293 A	03-09-1993
		CA 2129112 A1	19-08-1993
WO 9320071	A	14-10-1993	AT 188697 T
		AU 3949793 A	15-01-2000
		CA 2133083 A1	08-11-1993
		CN 1081677 A	14-10-1993
		CZ 9402368 A3	09-02-1994
		DE 69327583 D1	13-09-1995
		DE 69327583 T2	17-02-2000
		DK 640081 T3	31-05-2000
		WO 9320071 A1	19-06-2000
		EP 0640081 A1	14-10-1993
		EP 0972773 A1	01-03-1995
		ES 2141763 T3	19-01-2000
		FI 944513 A	01-04-2000
		GR 3032877 T3	29-11-1994
		HU 72321 A2	31-07-2000
		JP 3236298 B2	29-04-1996
		JP 7505868 T	10-12-2001
		MX 9301837 A1	29-06-1995
		NO 943631 A	28-02-1994
		NZ 251687 A	29-11-1994
WO 9116045	A	31-10-1991	PT 640081 T
		SK 116394 A3	21-12-1995
		US 5618827 A	31-05-2000
		ZA 9302306 A	12-04-1995
		AT 181668 T	08-04-1997
		AU 653521 B2	30-09-1994
		AU 7768091 A	
		CA 2081344 A1	
		DE 69131398 D1	
		DE 69131398 T2	
			DK 526540 T3
			EP 0526540 A1
			ES 2134774 T3
			WO 9116045 A2
			GR 3031042 T3
			IE 911383 A1
			06-11-1991

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 01/03544

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9116045	A	JP 5509293 T	22-12-1993
		PT 97477 A ,B	31-01-1992
		ZA 9103071 A	25-11-1992